Stereocontrolled Total Synthesis of (+)-K252a

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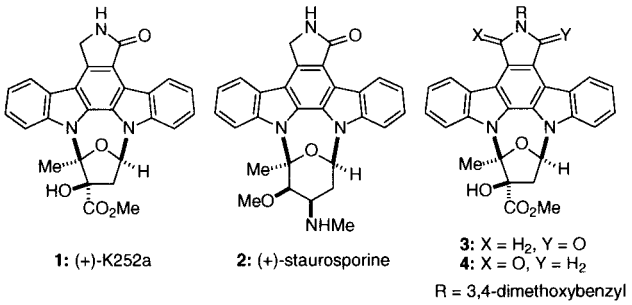
The structurally related indolocarbazole alkaloids (+)-K252a[1,2] (**1**) and (+)-staurosporine[3] (**2**) have attracted considerable attention due to the unique asymmetrical structure of the cycloglycoside moieties as well as the strong PKC inhibitory activity. Many efforts have been directed toward the regioselective synthesis of the N-monoprotected aglycon moiety of K252a.[4] While Wood and co-workers have recently completed an efficient total synthesis of (+)-K252a,[5] they failed to solve the regiochemical problem of the cycloglycosidation, resulting in the formation of a 2:1 mixture of the desired product **3** and its regioisomer **4**. In

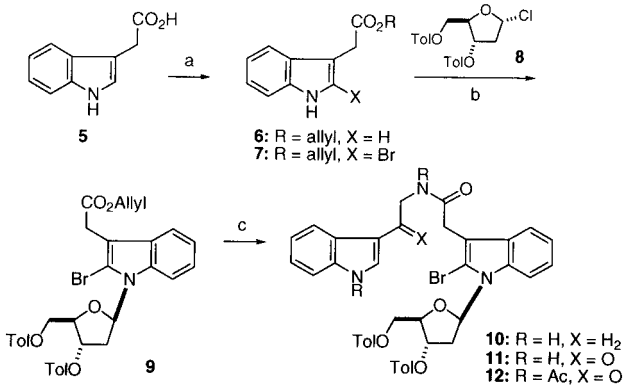


their total synthesis of (+)-staurosporine, Danishefsky and co-workers also obtained a 1:1 mixture of the regioisomeric intermediates.[6] Herein we report a completely stereocontrolled total synthesis of (+)-K252a, which is applicable to the synthesis of a range of indolocarbazolyl glycosides.

Regiospecific bromination[7] of indole **6**, prepared by allylation of indole-3-acetic acid (**5**), was performed by treatment with NBS to give 2-bromoindole **7** (Scheme 1). N-Glycosidation[8] of the indole **7** was carried out by deprotonation with sodium hydride, followed by addition of readily available 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose[9] (**8**) to give β-N-glycoside **9** as the sole product. After deprotection of the allyl ester **9**, the acid which resulted was condensed with tryptamine under conventional conditions to give amide **10**. Regioselective oxidation of the more reactive indole of **10** with 2 equiv of DDQ in aqueous THF afforded the ketone **11** exclusively.[10] For the ensuing cyclization, the ketone and the amide in **11** were both activated by acetylation of the indole and amide nitrogens to give diacetyl bisindole.[11]

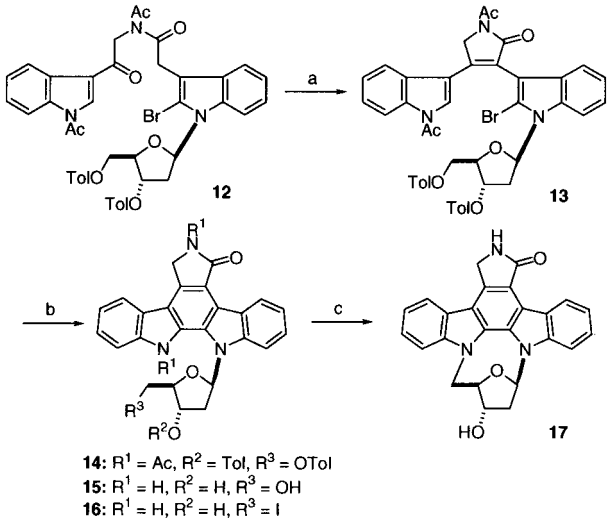
Upon treatment with a catalytic amount of DBU and molecular sieves, **12** underwent smooth cyclization to give lactam **13** (Scheme 2).[12] A nonoxidative photocyclization[13] was performed by exposing lactam **13** to sunlight[14] in the presence of diisopro-

Scheme 1[a]



[a] Reagents and yields: (a) allyl bromide, K_2CO_3, DMF, 23 °C, 100 min, 99%; (b) (i) NBS, CCl_4, 23 °C, 90 min, 80%; (ii) NaH, MeCN, 23 °C, 10 min; **8**, 23 °C, 30 min, 97%; (c) (i) $Pd(PPh_3)_4$, Ph_3P, pyrrolidine, CH_2Cl_2, 23 °C, 1 h; (ii) WSCD, tryptamine, CH_2Cl_2, 23 °C, 15 min, 72% (2 steps); (iii) DDQ (2.2 equiv), THF/H_2O (9:1), 0 °C, 30 min, 93%; (iv) 2,6-lutidine (2 equiv), DMAP (0.2 equiv), Ac_2O, 60 °C, 8 h, 78%.

Scheme 2[a]



[a] Reagents and yields: (a) DBU (0.1 equiv), MS 4 Å, THF, 60 °C, 2.5 h, 92%; (b) *i*-Pr_2NEt, *hν*, CH_2Cl_2 (2.8×10^{-2} M), 23 °C, 5 h, 96%; (c) (i) KOH, H_2O/MeOH/THF, 23 °C, 45 min, 97%; (ii) I_2, Ph_3P, imidazole, THF, 23 °C, 1 h, 82%; (iii) DBU, THF, 80 °C.

(1) (+)-K252a was isolated independently by two Japanese groups. (a) Sezaki, M.; Sasaki, T.; Nakazawa, T.; Takeda, U.; Iwata, M.; Watanabe, T.; Koyama, M.; Kai, F.; Shomura, T.; Kojima, M. *J. Antibiot.* **1985**, *38*, 1439. (b) Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiot.* **1986**, *39*, 1059.

(2) For structure elucidation of (+)-K252a, see: (a) Nakanishi, S.; Matsuda, Y.; Iwahashi, K.; Kase, H. *J. Antibiot.* **1986**, *39*, 1066. (b) Yasuzawa, T.; Iida, T.; Yoshida, M.; Hirayama, M.; Takahashi, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1986**, *39*, 1072.

(3) For isolation and structure elucidation of (+)-staurosporine, see: (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275. (b) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *J. Chem. Soc., Chem. Commun.* **1978**, 800. (c) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3681.

(4) (a) Magnus, P. D.; Sear, N. L. *Tetrahedron* **1984**, *40*, 2797. (b) Brüning, J.; Hache, T.; Winterfeldt, E. *Synthesis* **1994**, 25. (c) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043.

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(6) (a) Link, J. L.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552. (b) Link, J. L.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825.

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(10) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.

(11) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469.

(12) Lactam **13** exists as a 1:1 mixture of atropisomers.

(13) For an example of a nonoxidative photochemical synthesis of phenanthrenes, see: Cava, M. P.; Mitchell, M. J.; Havlicek, S. C.; Lindert, A.; Spangler, R. J. *J. Org. Chem.* **1970**, *35*, 175.

(14) A 500-W halogen lamp can be used in laboratories.

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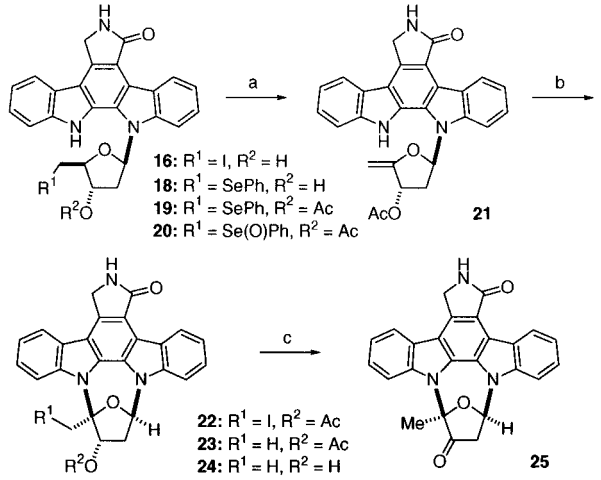
Scheme 3[a]

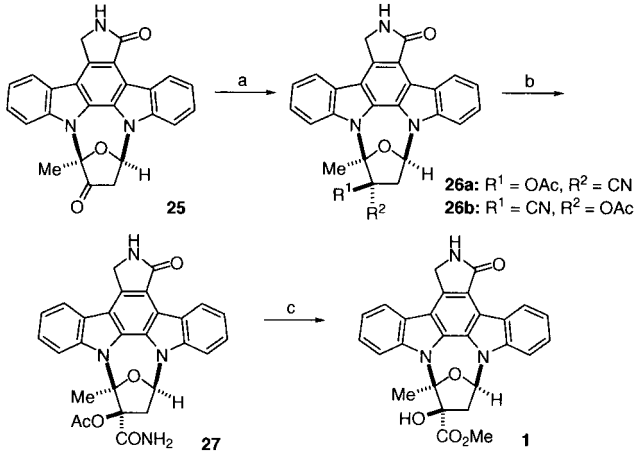


[a] Reagents and yields: (a) (i) PhSeSePh, $NaBH_4$, EtOH/THF (2:5), 23 °C, 93%; (ii) Ac_2O, Py, DMAP, 23 °C, 10 min, 98%; (iii) *m*-CPBA, THF, 23 °C, 10 min; NEt_3, DHP, 80 °C, 30 min, 91% (2 steps); (b) KI (6 equiv), I_2 (5 equiv), DBU (2 equiv), THF, 23 °C, 40 min, 93%; (c) (i) *n*-Bu_3SnH, AIBN, MeCN, reflux, 50 min, 98%; (ii) K_2CO_3, MeOH, 23 °C, 10 min, 90%; (iii) DCC (6 equiv), Cl_2CHCO_2H (2 equiv), DMSO, 23 °C, 15 min, 99%.

pylethylamine to provide the desired indolocarbazole **14** in near quantitative yield. Without doubt, the photochemically induced conversion was promoted by the facile dehydrobromination of the incipient cyclization product.[15] Following hydrolysis of all the acyl groups in **14**, the primary alcohol was selectively converted to the corresponding iodide **16** by treatment with iodine, triphenylphosphine, and imidazole.[16] Attempts to dehydroiodinate **16** failed to give the desired olefin, and only the undesired cycloglycoside **17** was obtained.

Conversion of iodide **16** to olefin **21** was effected by the conventional, four-step sequence shown in Scheme 3.[17] Much to our dismay, initial attempts to construct the desired cycloglycoside from the enol ether **21** under oxidative or acidic conditions failed.[18] Treatment of **21** with potassium *tert*-butoxide and iodine, used successfully by Danishefsky in their total synthesis of staurosporine,[6] gave the desired cycloglycoside **22** in less than 10% yield. However, upon treatment with iodine, potassium iodide, and DBU, **21** underwent a remarkably smooth iodoglycosidation to give the required cycloglycoside **22** in 93% yield.[19] Radical-mediated deiodination,[20] methanolysis of the acetate, and the subsequent oxidation of the alcohol **24** with DCC, Cl_2CHCO_2H, and DMSO furnished ketone **25** in high yield.

Scheme 4[a]



[a] Reagents and yields: (a) HCN (xs), Py (xs), MeCN, 0 °C, 15 min; Ac_2O, DMAP, 23 °C, 30 min, 99%; (b) HCl, HCO_2H, 23 °C, 19 h, 88%; (c) (i) KOH, H_2O/MeOH/THF, 100 °C, 10 h; (ii) CH_2N_2, THF, 65% (2 steps).

Transformation of the ketone **25** into the corresponding cyanohydrin under ordinary conditions resulted in the formation of a diastereomeric mixture. However, only the desired, kinetically favored cyanohydrin acetate **26a** was obtained when treated with hydrogen cyanide and pyridine,[21] followed by acetylation.[22] Since attempted conversion of **26a** to **1** in methanolic HCl gave primarily ketone **25** along with a trace amount of the desired **1**, an indirect procedure was adopted. Namely, the nitrile **26a** was first converted to amide **27** by treatment with gaseous HCl in formic acid at room temperature.[23] Finally, the amide **27** was subjected to alkaline hydrolysis and the resultant acid esterified with diazomethane to give (+)-K252a (**1**) (Scheme 4). The synthetic (+)-K252a proved to be identical with the natural product[24] in TLC behavior as well as in spectroscopic properties (^1H, ^{13}C NMR, IR, MS, $[\alpha]_D$).

In conclusion, the stereocontrolled total synthesis of (+)-K252a has been achieved in a 23-step sequence from indole-3-acetic acid with an overall yield of 10%. The established synthetic route should be amenable to the preparation of a variety of interesting analogues.

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Supporting Information Available: Listing of spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For syntheses of indolocarbazoles by means of less effective, oxidative photocyclization, see: (a) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015. (b) Weinreb, S. M.; Garigipati, R. S.; Gainor, J. A. *Heterocycles* **1984**, *21*, 309. (c) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361. (d) Xie, G.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555. (e) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469. (f) Brüning, J.; Hache, T.; Winterfeldt, E. *Synthesis* **1994**, 25.

(16) Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* **1988**, *53*, 6126.

(17) For the selenoxide elimination step, triethylamine and DHP were added to prevent the undesired oxidative addtion of phenylselenous acid to the reactive enol ether.

(18) Several oxidizing agents including *m*-CPBA, 3,3-dimethyldioxirane, $PdCl_2$, $Hg(OAc)_2$, NBS, NIS, bromine, iodine, ICl, bromopyridinium pyridine tetrafluoroborate, and acid catalysts such as CSA, PPTS, and Amberlyst were examined. Under these conditions, **21** suffered extensive decomposition.

(19) The success of this cycloglycosidation might be attributable to the attenuated reactivity of the oxidizing agent, KI_3, and the heightened HOMO level of the enol ether due to the proximate indolyl anion, enabling a concerted reaction to take place.

(20) Kuivila, H. G.; Menapace, L. W. *J. Org. Chem.* **1963**, *28*, 2165.

(21) Use of more basic triethylamine as a base gave, after acetylation, a 3:1 mixture of **26a** and **26b**.

(22) The unprotected cyanohydrin was prone to lose hydrogen cyanide to give ketone **25**.

(23) Becke, F.; Fleig, H.; Pässler, P. *Liebigs Ann. Chem.* **1971**, *749*, 198.

(24) We are indebted to Dr. C. Murakata of Kyowa Hakko Kogyo for a generous gift of natural (+)-K252a.